Research on Ethical Issues in Human Studies

NIH invites research grant applications to investigate ethical issues in research using human subjects. The *Code of Federal Regulations* (45 CFR, Part 46) provides a regulatory framework that all NIH-supported researchers must follow. However, recent developments in biomedical and behavioral research—including the rapid growth of new interventions and technologies (e.g., stem cells, genetics research), increasing involvement of foreign populations in clinical research, and concerns about financial conflicts of interest among researchers—challenge investigators' abilities to interpret and apply the regulations. Other situations (e.g., research with vulnerable populations, the use of data banks or archives, research on stigmatizing diseases or conditions) may present difficulties for identifying strategies, procedures, and/or techniques that will enhance and ensure the ethical involvement of human participants in research.

The purpose of this PA is to support empirical research addressing the ethical challenges of involving human participants in research in order to inform and optimize protections for human participation in research. Examples of the types of topics that would be appropriate for applications submitted under this announcement include, but are not limited to, the following:

Minimizing Risks in Human Research

1) Assess how features of the research and research setting affect evaluations of risks versus potential benefits of different types of research for investigators, institutional review board (IRB) members, and potential participants, groups, and communities. Examples of features of the research or research setting may include characteristics of the participants (e.g., age, health status and stage of disease, ethnic/cultural background, cognitive capacity, social status, gender, incarceration), aspects of the condition/disease (e.g., prevalence, severity, chronicity, degree of disability), and the nation or culture in which the study will take place.

2) Identify potential social, psychological, and/or economic harms (e.g., stigma, discrimination, personal distress, loss of insurance coverage, loss of employment) that may be associated with recruitment, participation, or self-determined or study-determined withdrawal from research. Evaluate strategies or procedures for minimizing these harms in regard to individuals', groups', communities', and populations' willingness to participate in different types of research.

3) Assess the conditions and assumptions under which IRB evaluation of risk versus potential benefits is similar to or different from the evaluation of risks versus potential benefits by individuals, groups, communities, and populations.

4) Assess the impact of obtaining a certificate of confidentiality on perceptions of IRB members and/or participants in terms of evaluation of risks, understanding of the research, and/or understanding of the rights to privacy.

5) Identify and evaluate strategies for protecting and minimizing disclosure of private information when identifiable data are collected via the Internet, preserved for secondary analysis (e.g., in a tissue or gene bank, data archive, warehouse), and/or collected about third parties in research (e.g., network studies).

Issues in Informed Consent

1) Determine how features of the informed consent process affect participants' comprehension and/or willingness to participate in research. Examples of these features include a) variations in the style of presentation (e.g., oral, written, graphic, video); b) readability, complexity, and/or format of the consent document; c) characteristics of the participants (e.g., language preference, age, health status, education, cultural/ethnic background, personal motivations, cognitive capacity); and d) contextual features or circumstances in which informed consent takes place (e.g., characteristics of the research staff, location such as research hospital versus private office versus home, presence/involvement of family members, presence/involvement of patient advocates).

2) Evaluate different methods and identify best-practice strategies for consulting with communities in the United States and/or other countries regarding comprehension, willingness to participate, and/or willingness to continue with research at the individual, group, community, and/or population level.

3) Assess how recontacting participants to obtain informed consent for additional uses of their data affects participant comprehension, willingness to participate, and sense of coercion.

4) Identify and evaluate strategies, procedures, and/or techniques for improving comprehension of research by individuals, groups, communities, and/or populations at the time of initial consent, during, and/or after completion of the study. Also, determine how these strategies may differ depending on age, health status, ethnic/cultural background, cognitive capacity, social status, and/or gender of the target audience.

5) Assess how participants' willingness to participate versus sense of coercion, may be affected by use of different types of incentives, remuneration, and/or provision of medical care; different features of the research setting (e.g., personal physician as recruiter and/or researcher, private funding versus federal funding); and characteristics of the participants (e.g., health status, age, ethnic/cultural background, education, gender).

6) Assess the impact of communicating or not communicating individual test results, study progress, and/or study results on participants' willingness to continue with the protocol and/or participate in research again.

Oversight of Research and Research Data

1) Identify and evaluate strategies to improve the oversight of human participants protection by IRBs, data and safety monitoring boards (DSMB), conflict of interest (COI) committees, etc. Examples may include a) develop and evaluate best-practice outcome measures for decision making about the acceptability of research protocols; b) assess the consistency of protocol review decisions within DSMBs, IRBs, or COI committees; c) assess the impact of conflicts of interest among members of oversight committees on decision making about the acceptability of research protocols, interpretations of adverse events, and/or perceptions of "independence of review" by the research community; and d) assess the impact of disclosing varying degrees of financial conflicts of interest involving the principal investigator, members of oversight committees, sponsor, institution, etc. on research participant willingness to participate and/or continue with research, and/or participant understanding of the research.

2) Compare and evaluate different methods and strategies for identifying, reporting, and handling adverse events based on the perspectives of individual participants, institutions, DSMBs, and/or IRBs.

This PA will use the NIH R01 award mechanism and Just in Time concepts. It will also use the modular as well as the nonmodular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for nonmodular research grant applications.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Complete information on this PA is available at http://grants1.nih.gov/grants/guide/pa-files/PA-02-103.html. To assist in identifying which NIH institute/office most closely matches your research topic, the following website provides additional information about institute- and office-specific research interests that will be supported by this PA: http://grants.nih.gov/grants/funding/ethics_contacts.htm.

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Environmentally Induced Cardiovascular Malformations

The NIEHS invites applications to study environmental agents that cause cardiovascular malformations (CVMs). This PA is intended to stimulate research to characterize environmental agents that cause alterations in the development of the cardiovascular system and thereby lead to CVMs, and to investigate the cellular and molecular mechanisms involved in the development of these CVMs. The use of mammalian and nonmammalian animal models, including transgenic and gene knockout animal models, and of state-of-the-art molecular biology techniques such as genomics and proteomics is encouraged, as well as collaborations between environmental health scientists and developmental biologists, to develop research programs to address the high rate of CVMs.

CVMs are the most common type of birth defect among live births in the United States, occurring in approximately 0.8% of live births. The most common types of CVMs include atrial or ventricular septal defects, transposition of the great vessels, persistent truncus arteriosus, teratology of Fallot, and coarctations. Despite the importance of these in malformations, in terms both of human suffering and cost to the health care system, the causes of most cases of CVMs are not known.

Etiologic factors that have been identified include genetics, maternal diseases such as diabetes, certain drugs such as phenytoin and cocaine, and dietary factors such as folic acid deficiency, vitamin A excess, and copper deficiency. In addition, certain environmental chemicals have been shown to be associated with CVMs. For instance, in the Baltimore–Washington Infant Study, a large epidemiologic study of cardiac malformations, exposure to such environmental factors as paints, solvents, degreasers, and pesticides was associated with increased CVMs.

Epidemiologic studies have also reported CVM associations with air pollutants (ozone and carbon monoxide) and trichloroethylene (TCE). In addition, environmental contaminants such as TCE, bisdiamine, and dioxin have been shown to be cardiac teratogens in animal studies.

Despite the evidence for an environmental role in CVMs, the list of environmental agents tested for teratogenic effects on the heart is limited, and relatively little research has been done on the cellular and molecular basis of the teratogenic effects of environmental

agents or on the possible interactions between environmental exposures and other factors such as diet and genetics. Recent advances in genomic and molecular biology technology and in the understanding of the development of the fetal heart make this an opportune time to initiate such studies.

Specific areas of interest to the NIEHS include, but are not limited to, the following: 1) characterization of new potential environmental cardioteratogens that would include the types of CVMs induced, dose–response evaluation, identification of specific windows of vulnerability to the agent, and development of preliminary data for further mechanistic studies; 2) use of forward and reverse mutagenesis studies in model organisms to determine the genes altered by specific cardiovascular developmental toxicants and the relationship of the altered gene activity to dysmorphogenesis; 3) characterization of global gene expression profiles in the developing heart of model organisms associated with the normal range of development and after a developmentally toxic exposure (the relationship between the changes in gene expression and the developmental lesion should be assessed); 4) use of genomic and/or proteomic profiling to determine how well data on toxicant-induced malformations can be extrapolated across species; 5) identification and evaluation of specific signal transduction pathways and the associated genetic regulatory circuits that might be sites of action of developmental cardiovascular toxicants (the causal relationships between exposure and the CVMs should be developed); and 6) determination of the potential for interactions between exposures to environmental agents and genetic susceptibility that increase the risk for cardiovascular developmental toxicity.

This PA will use the NIH R21 and R01 award mechanism(s). Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines, which are indicated in the PHS 398 application kit. Complete information on this PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-02093.html.

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The Role of Gene–Environment Interactions Underlying the Health Disparity of Premature Birth

The National Institute of Child Health and Human Development (NICHD), the National Institute of Nursing Research (NINR), and the NIEHS are seeking research grant applications on the role of gene–environment interactions underlying the health disparity of premature birth in the United States. The major objective of this PA is to determine the role of gene–environment interactions and genetic diversity in the health disparity of premature birth. This PA specifically addresses the need to better understand how adverse societal, behavioral, and environmental conditions alter gene expression and interact with diverse genetic backgrounds to increase a woman's susceptibility for premature birth in high-risk racial and ethnic groups in the United States. Furthermore, the PA addresses the need for the identification and functional characterization of genetic markers that increase the risk of premature birth among these high-risk populations. Multidisciplinary applications linking biomedical scientists with social and behavioral scientists are highly encouraged.

This PA seeks research projects focused on one or more of the following goals:

1) Determine changes in gene or protein expression under adverse societal, behavioral, or environmental conditions to identify candidate genes or their corresponding proteins that may be involved in increasing a woman's susceptibility for premature delivery in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies utilizing gene or protein expression profiling by high-throughput platforms, such as DNA arrays, protein arrays, and protein capture/SELDI-TOF mass spectrometry.

2) Determine the functional relevance of an identified gene or protein for increasing a woman's susceptibility for premature delivery under adverse societal, behavioral, or environmental conditions in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies elucidating the function or mechanism of action of an identified gene or protein in precipitating premature delivery.

3) Determine genomic differences that serve as potential candidate markers for increasing a woman's susceptibility for premature delivery under adverse societal, behavioral, or environmental conditions in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, linkage studies using high-throughput genotyping platforms to uncover genomic differences, such as sequence repeats and multiple or single nucleotide polymorphisms.

4) Determine the functional relevance of candidate genomic markers associated with an increased risk for premature birth in high-risk racial and ethnic populations in the United States. Examples include, but are not limited to, studies that determine the functional consequence of these markers as it relates to gene expression, function, or regulation.

Applicants are encouraged to consider the complexity of issues surrounding the meaning and assessment of race and ethnicity, because an individual's identification with a particular racial or ethnic group may involve not only an individual's genetic background but also his or her cultural and geographical identity. As appropriate for their particular proposals, applicants should consider the degree of genomic heterogeneity within racial and ethnic populations and that genetic differences may not apply broadly to a specific race or ethnic group, and should consider the new Office of Management and Budget (OMB) directives on classifying race and ethnicity. NIH policy on reporting race and ethnicity data based on OMB directives is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

Because the NIEHS has expanded its research agenda through the Environmental Genome Project, the NIEHS is particularly interested in applications that examine the complex interplay of genes and the environment. The understanding of the critical role of genetic susceptibility and sensitivity to environmental exposures will lead to more effective disease prevention and improved public health.

This PA will use the NIH research project grant (R01) award mechanism. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines indicated in the PHS 398 application kit. Complete information on this PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-02-102.html.

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